

**TRANSMITTAL LETTER TO THE UNITED STATES  
DESIGNATED/ELECTED OFFICE (DO/EO/US)  
CONCERNING A FILING UNDER 35 U.S.C. 371**

SCH 1655

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

**99/117357**

INTERNATIONAL APPLICATION NO.

PCT/EP97/00395

INTERNATIONAL FILING DATE

29 January 1997

PRIORITY DATE CLAIMED

29 January 1996

TITLE OF INVENTION PHARMACEUTICAL COMBINED PREPARATION AND ITS USE IN THE TREATMENT  
OF GYNAECOLOGICAL DISORDERS

APPLICANT(S) FOR DO/EO/US

STOCKEMANN, Klaus, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.  
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

A Letter regarding the Article 34 Amendments is attached.

PCT/EP97/00395

SCH 1655

17. ☒ The following fees are submitted:**BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)):**

Search Report has been prepared by the EPO or JPO ..... \$ 930.00

International preliminary examination fee paid to USPTO (37 CFR 1.482)  
..... \$ 720.00No international preliminary examination fee paid to USPTO (37 CFR 1.482)  
but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... \$ 790.00Neither international preliminary examination fee (37 CFR 1.482) nor  
international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$ 1070.00International preliminary examination fee paid to USPTO (37 CFR 1.482)  
and all claims satisfied provisions of PCT Article 33(2)-(4) ..... \$ 98.00**ENTER APPROPRIATE BASIC FEE AMOUNT =****CALCULATIONS PTO USE ONLY**

\$ 930.00

Surcharge of \$130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30  
months from the earliest claimed priority date (37 CFR 1.492(e)).

\$ 130.00

| CLAIMS             | NUMBER FILED | NUMBER EXTRA | RATE       |
|--------------------|--------------|--------------|------------|
| Total claims       | 15 - 20 =    | 0            | X \$ 22.00 |
| Independent claims | 4 - 3 =      | 1            | X \$ 82.00 |

\$ 0.00

\$ 82.00

MULTIPLE DEPENDENT CLAIM(S) (if applicable) + \$ 270.00

\$

**TOTAL OF ABOVE CALCULATIONS =**

\$ 1,142.00

Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement  
must also be filed (Note 37 CFR 1.9, 1.27, 1.28).

\$

**SUBTOTAL =**

\$ 1,142.00

Processing fee of \$130.00 for furnishing the English translation later than ☐ 20 ☐ 30  
months from the earliest claimed priority date (37 CFR 1.492(f)).

\$

**TOTAL NATIONAL FEE =**

\$ 1,142.00

Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be  
accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +

\$

**TOTAL FEES ENCLOSED =**

\$ 1,142.00

Amount to be:  
refunded

\$

charged

\$

a. ☒ A check in the amount of \$ 1,142.00 to cover the above fees is enclosed.b. ☐ Please charge my Deposit Account No. \_\_\_\_\_ in the amount of \$ \_\_\_\_\_ to cover the above fees.  
A duplicate copy of this sheet is enclosed.c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any  
overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.**NOTE:** Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.  
Arlington Courthouse Plaza I  
2200 Clarendon Boulevard, Suite 1400  
Arlington, Virginia 22201  
(703) 243-6333

SIGNATURE

Anthony J. Zelano

NAME

27,969

REGISTRATION NUMBER

Filed: 28 July 1998

AJZ:kdm

## IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No. : PCT/EP97/00395

International Filing Date : 29 January 1997

Priority Date Claimed : 29 January 1996

Applicant(s) (DO/EO/US) : STÖCKEMANN, Klaus, et al.

Title: PHARMACEUTICAL COMBINED PREPARATION AND ITS USE IN THE  
TREATMENT OF GYNAECOLOGICAL DISORDERS

**PRELIMINARY AMENDMENT**

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend this application as follows:

**IN THE SPECIFICATION:**

- Page 3, line 27:** Change "Cit-Leu-Lys(Mor)-D-Ala-NH<sub>2</sub>)," to  
-- Cit-Leu-Lys(Mor)-Pro-D-Ala-NH<sub>2</sub>), --.
- Page 11, line 6:** Delete the line in its entirety and replace it with the following:  
-- Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Lys(Mor)-Pro-D-Ala- --.

**IN THE CLAIMS:**

Please amend claims 3-9 as follows:

- Claim 3, line 1:** Delete "or 2"; and  
**line 5:** Change "Leu-Lys(Mor)-D-Ala-NH<sub>2</sub>," to  
-- Leu-Lys(Mor)-Pro-D-Ala-NH<sub>2</sub>, --.
- Claim 4, line 1:** Change "any one of claims 1" to -- claim 1, --; and  
**line 2:** Delete "to 3,".

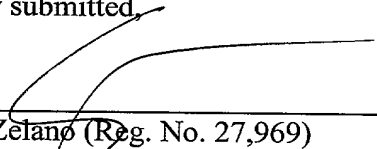
09/11/7357

- Claim 5, line 1:** Change "any one of claims 1" to -- claim 1, --; and  
**line 2:** Delete "to 4,".
- Claim 6, line 1:** Change "any one of claims 1" to -- claim 1, --; and  
**line 2:** Delete "to 5,".
- Claim 7, line 1:** Change "any one of claims 1" to -- claim 1, --; and  
**line 2:** Delete "to 6,".
- Claim 8, line 1:** Change "any one of claims 1" to -- claim 1, --;  
**line 2:** Delete "to 7,"; and  
**line 3:** Change "separate" to -- common --.
- Claim 9, line 1:** Change "any one of claims 1" to -- claim 1, --; and  
**line 2:** Delete "to 7,".

### REMARKS

The principal purpose of this Preliminary Amendment is to eliminate multiple dependencies in order to avoid extra fees. In addition, typographical errors have been corrected at pages 3 and 11 of the specification and in claims 3 and 8.

Respectfully submitted,

  
\_\_\_\_\_  
Anthony J. Zelano (Reg. No. 27,969)  
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.  
Arlington Courthouse Plaza I  
2200 Clarendon Boulevard, Suite 1400  
Arlington, Virginia 22201  
Direct Dial: (703) 812-5311  
Facsimile: (703) 243-6410  
Internet Address: zelanoa@mwzb.com

Filed: 28 July 1998

AJZ:kd  
K:\PAT\Sch\1655\prel amd.wpd

**Pharmaceutical combined preparation and its use in the treatment of gynaecological disorders**

The invention relates to a pharmaceutical combined preparation of LHRH analogues and anti-oestrogens having a tissue-selective oestrogenic activity, and also to its use for the treatment of gynaecological disorders, especially for the treatment of endometrioses and myomas.

Gynaecological disorders and diseases considerably reduce the quality of life of women and frequently result, in some cases in addition to unbearable pain, in infertility. One of the most common diseases in women of child-bearing age (5 % to 10 %) is endometriosis. Associated with it are severe pain during menstruation and a limited fertility rate to sterility. In the case of the myoma, a benign tumour in the muscle tissue of the uterus, the incidence is high too (in 10 to 25 % of women in their 30s). Myomas may cause heavy abnormal menstrual bleeding (hypermenorrhoea), painful menstruation (dysmenorrhoea) and/or intermenstrual bleeding (metrorrhagia, menorrhagia) and each, depending on the condition, may also result in limited fertility. In addition to dysmenorrhoea caused by endometriosis and by myomas, dysmenorrhoea that is caused by functional disorders (by hormonal and vegetative disorders) also occurs.

The gonad steroids (oestrogens, gestagens), which are under the control of the hypothalamic-pituitary system, and growth factors (including also cytokines) play a decisive role in the clinical syndromes described. Treatment of such diseases and disorders is usually effected with hormones, such as LHRH analogues (Lemay, A. et al., Fertil. Steril., 41, 863-871 (1984)). In some women, however, these are not tolerated without side effects. For example, it is known that treatment with LHRH

agonists may result in side effects such as, for example, hypo-oestrogenaemia (risk of osteoporosis) (Dawood, M.Y. et al., Fertil. Steril. 52, 21-25, (1989)) and treatment with danazol may result in androgenisation phenomena (Dmowski, W.P. et al., Am. J. Obstet. Gynecol., 130, 41-48 (1978)).

No established and proven long-term medicament treatment has existed hitherto for myomas. The medicament treatment currently used is associated with distinct side effects. For example, the use of LHRH agonists for more than six months results in a hypo-oestrogenic state in women (Matta, W.H. et al., Br. Med. J., 294, 1523-1525, (1987)) and, associated with that, a reduction in bone density, which increases the risk of osteoporosis (Dawood, M.Y. Int. J. Gynecol. Obstet., 40, 29-42 (1993)). Other side effects associated with oestrogen withdrawal (hot flushes) are also described by Dawood.

Studies for the treatment of gynaecological disorders with LHRH analogues and oestrogens - so-called Add-Back or HRT treatment regimes - are known for the purpose of avoiding those side effects. The discovery of an oestrogen dose that completely prevents a reduction in bone density using LHRH agonist therapy (Howell, R. et al., Fertil. Steril. 64, 474-481, (1995)) without at the same time stimulating endometriosis or stimulating the endometrium, which may result in endometrium hyperplasia and, associated with that, endometrium carcinomas, has hitherto been unsuccessful, however.

The problem underlying the invention is therefore to prepare a pharmaceutical combined preparation for the treatment of gynaecological disorders, especially for the treatment of endometrioses and myomas, with which a reduction in bone density is prevented and the dis-

advantages of previous hormone treatments are avoided.

The problem is solved in accordance with the invention by a pharmaceutical combined preparation that comprises two active ingredients, the first of which is an LHRH analogue or a combination of LHRH analogues and the second of which is an anti-oestrogen having tissue-selective oestrogenic activity.

The LHRH analogue is an LHRH agonist or antagonist.

Any LHRH antagonist or LHRH agonist may be used within the scope of the invention. Preferred LHRH analogues are selected from the group of compounds Leuprorelin, Cetrorelix, Antide, Buserelin, Ramorelix, Zoladex, 2-(4-acetylamino-phenyl)-4,7-dihydro-7-(2-methoxybenzyl)-3-(N-methyl-N-benzylaminomethyl)-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ethyl ester and 5-benzoyl-7-(2,6-difluorobenzyl)-4,7-dihydro-3-(N-methyl-N-benzylaminomethyl)-2-(4-propionylamidophenyl)-4-oxothieno[2,3-b]pyridine.

The active ingredients are generally in separate forms of administration or, in the case of orally bioavailable LHRH antagonists, also in a joint form of administration.

The LHRH analogues preferably used are known and are described in the patent specifications US 4 005 063 (Leuprorelin), EP-B1 0 299 402 (Cetrorelix), GB 1 523 623 (Buserelin), EP-A 0 451 791 (Ramorelix), WO-A 89/01944 (Antide), WO-A 92/20711 (Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Lys(Mor)-D-Ala-NH<sub>2</sub>), US 4 100 274 (Zoladex) and WO-A 95/28405 (2-(4-acetylamino-phenyl)-4,7-dihydro-7-(2-methoxybenzyl)-3-(N-methyl-N-benzylaminomethyl)-4-oxothieno[2,3-b]pyridine-5-carboxylic acid ethyl ester).

They are prepared and packaged according to processes known per se and, depending on the desired use, are available in oral or nasal form, in the form of an injection, or in the form of a long-term preparation to be administered topically or intravaginally. According to the invention, the LHRH analogues may be administered as individual doses or as depot forms.

A unit dose contains different amounts of active ingredient depending in each case on the form of administration. For example, in the case of oral administration usually from 2  $\mu\text{g}$  to 20 mg of LHRH analogue is administered per kg of body weight. The administration may be in solid or liquid form. For intravenous, subcutaneous, intramuscular, intranasal or intravaginal administration, the amounts of LHRH analogues are from 0.02  $\mu\text{g}$  to 2.5 mg per kg of body weight. For parenteral administration there is preferably used an isotonic sodium chloride or dextrose solution that optionally is adjusted with a buffer to a pH value of from 5 to 9, preferably to the pH value of the blood.

Leuprorelin is preferably used orally at a dose of from 2 to 100  $\mu\text{g}/\text{kg}$  of body weight (daily dose); one tablet contains preferably from 0.1 to 5.0 mg of Leuprorelin. The dose for parenteral administration is preferably from 0.02 to 1.0  $\mu\text{g}/\text{kg}$  of body weight.

Cetrorelix is used preferably in the form of a physiological saline with an amount of active ingredient of from 0.1 to 2.5 mg/kg of body weight. In DE 43 42 092, also slow-release formulations of Cetrorelix are described.

Buserelin is administered preferably in the following doses :



from 0.02 to 1  $\mu\text{g/kg}$  of body weight (intravenous),  
from 0.02 to 2  $\mu\text{g/kg}$  of body weight (subcutaneous),  
from 0.02 to 10  $\mu\text{g/kg}$  of body weight (intramuscular),  
from 0.1 to 50  $\mu\text{g/kg}$  of body weight (intranasal) and  
from 10 to 200  $\mu\text{g/kg}$  of body weight (oral).

As in the case of Cetrorelix, slow-release formulations are also possible. In the case of an implant, the implant contains from 1 to 6 mg of Cetrorelix.

Zoladex is preferably administered orally with a content of from 50  $\mu\text{g}$  to 20 mg/kg of body weight and parenterally with a content of from 0.02  $\mu\text{g}$  to 100  $\mu\text{g/kg}$  of body weight or using a slow-release system (WO-A 93/24150).

Antide is, like Cetrorelix, administered in an amount of from 0.1 to 2.5 mg/kg of body weight.

The administration of Ramorelix is carried out preferably in liposomal form.

Depot formulations for peptides (microparticles, implants) are described inter alia in EP 0 505 966 and EP 0 315 875.

According to the invention, the second active ingredient component of the combined preparation is an anti-oestrogen having tissue-selective oestrogenic activity.

Anti-oestrogenic substances are used inter alia in tumour therapy.

Within the scope of the invention there are to be understood by anti-oestrogens having tissue-selective oestrogenic activity so-called SERMs (selective oestrogen-receptor modulators) which exert their partial

agonistic oestrogenic activity tissue- and organ-selectively.

Any antioestrogen having tissue-selective oestrogenic activity may be used in accordance with the invention. Preferably used are those selected from the group Raloxifen, Droloxifen, Centchroman and derivatives thereof. Anti-oestrogens of the Raloxifen type are especially preferred.

The anti-oestrogens mentioned are known. For example Raloxifen is 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene. In combination with parathyroid hormone, Raloxifen and its derivatives are used to increase bone mass (EP 0 635 270).

The active ingredient content of the anti-oestrogen used in accordance with the invention is in the case of daily administration from 0.1  $\mu$ g to 10 mg of antioestrogen per kg of body weight, depending on the form of administration. The anti-oestrogens may be administered intravenously, subcutaneously, intramuscularly, orally, intranasally or intravaginally. Slow-release formulations are also possible, in which case the amount released daily lies also within the above-mentioned range.

The administration of the LHRH analogue and of the anti-oestrogen to the patient may be simultaneous and/or chronologically sequential. Various treatment regimes are possible :

1. The LHRH analogue is administered simultaneously with the tissue-selective anti-oestrogen over the same period of time. Administration is possible daily, every three days, weekly or once monthly over a period of from 1 to 6 months. Longer administration is also readily possible.

05447357 1092298

In the case of monthly administration a depot formulation is preferred.

2. The LHRH analogue is first of all administered simultaneously with the tissue-selective anti-oestrogen over a particular period of time. The information given in 1 applies in respect of period and frequency of administration (daily or at greater intervals). Treatment is then continued with the anti-oestrogen only. Here, too, the information given in 1 applies in respect of period and frequency of administration.

3. The treatment with the LHRH analogue is conducted over a particular period of time and terminated. Following this the tissue-selective anti-oestrogen is then administered. For each component, the period and frequency of administration may be selected as indicated in 1.

It was established that the treatment with the combined preparation according to the invention surprisingly prevents the hitherto observed LHRH analogue-induced reduction in bone density, and the endometriosis, inhibited in its growth, is not stimulated again, and the growth of the normal endometrium in the uterus also is not stimulated.

The pharmaceutical combined preparation according to the invention is suitable especially for long-term treatment of endometrioses and myomas and other steroid(sex)-hormone-dependent disorders, since on the one hand the side effects that normally occur with an LHRH analogue (agonist or antagonist) treatment are avoided and on the other hand lost bone mass is rebuilt (for example in the case of administration of the tissue-selective anti-oestrogen after completion of an LHRH analogue treatment). At the same time the growth inhibition of the

endometriosis is maintained without the endometrium in the uterus being stimulated.

Variant 1 has proved especially preferred for long-term therapy.

The pharmaceutical combined preparation according to the invention is prepared, for example, by formulating the LHRH analogues and the anti-oestrogens having tissue-selective oestrogenic activity separately from one another with the customary pharmaceutical carriers, excipients and/or additives; the forms of administration of the individual active ingredients do not have to be identical. It is wholly possible, for example, for one active ingredient of the combined preparation to be administered orally while the other active ingredient is administered subcutaneously or nasally.

In the case of orally bioavailable LHRH analogues, it is also possible for the two active ingredients (LHRH analogues plus anti-oestrogen) to be formulated together for oral administration. Separate oral forms of administration are also possible.

The invention relates also to a packaging unit which, in the case of peptidergic LHRH analogues, comprises at least three components. The unit contains two spatially separately packaged active ingredients, one of which is an LHRH analogue or a combination of LHRH analogues, and the other of which is an anti-oestrogen having tissue-selective oestrogenic activity. The third component is an information leaflet for the simultaneous and/or chronologically sequential administration of the forms of administration.

The invention relates also to the use of an LHRH analogue

09117357.092299  
062260.25E7T60

or a combination of LHRH analogues and an anti-oestrogen having tissue-selective oestrogenic activity for the treatment of gynaecological disorders, especially for the treatment of endometrioses and myomas.

The invention is illustrated further in the following by Examples without, however, being limited to those Examples.

### Embodiment Examples

#### **Example 1**

Effect of LHRH administration and Raloxifen administration on experimentally produced endometriosis in the rat

- 1.1 Comparison of the administration of each of the active ingredient components alone with the simultaneous administration of the active ingredients (combined preparation)

#### **Method:**

Fragments of endometrium were transplanted into different regions of the abdominal cavity of 60 animals.

Four weeks later the development of the endometriosis (cystic endometriosis foci) was examined.

The animals were then treated for 4 weeks with the LHRH antagonists Antide (0.5 mg/animal every 3 days s.c.) and Raloxifen (3 mg/animal per day p.o.) in each case alone, or in a combination of the two compounds. At the end the size of the endometriosis foci before the beginning of the treatment was compared with the values after 4 weeks' treatment.

The combination of LHRH antagonist plus Raloxifen

resulted in a complete regression of the endometriosis without there being a significant reduction in bone mass. At the same time no oestrogenic effects on the uterus (no stimulation of the endometrium) were observed.

By comparison, although treatment with the LHRH antagonists alone resulted in a complete regression of the endometriosis foci, at the same time it caused a reduction in endogenous oestrogen levels corresponding to an ovariectomy. The result was a distinct reduction in bone density and an increase in osteoclast activity.

Administration of Raloxifen alone resulted in a partial regression of the endometriosis.

#### 1.2. LHRH antagonist Antide and Raloxifen for simultaneous and chronologically sequential administration

60 animals received the LHRH antagonist Antide and Raloxifen in parallel for the first 2 weeks and Raloxifen alone for the following 2 weeks. The doses were selected as in 1.1.

As with the simultaneous administration of the active ingredients, the result to be recorded was a complete regression of the endometriosis without a significant reduction in bone mass. At the same time there were no oestrogenic effects on the uterus.

#### 1.3. Chronologically sequential administration of the combined preparation

60 animals received the LHRH antagonist Antide for 2 weeks. On completion of the LHRH administration Raloxifen was then administered for 2 weeks.

This sequential treatment also resulted in 100 % regression of the endometriosis without a reduction in bone density.

Example 2

Analogously to Example 1, treatment with LHRH antagonists Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Lys(Mor)-D-Ala-NH<sub>2</sub> and Droloxifen was carried out on 40 animals.

The same results could be achieved as in Example 1.

202200/554780

1. Use of a LHRH analog or a combination of LHRH analogs and an antiestrogen with tissue-selective estrogenic effect which is selected from the group of compounds Raloxifen, Droloxifen, Centchroman, or their derivatives, for treatment of gynecological conditions, especially for treatment of endometrioses and myomas.

2. Use as claimed in claim 1, wherein the LHRH analog is a LHRH agonist or LHRH antagonist.

3. Use as claimed in claim 1 or 2, wherein the LHRH analog is selected from the group of compounds Leuprorelin, Centrorelax, Buserelin, Antide, Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Lys(Mor)-Pro-D-Ala-NH<sub>2</sub>, Ramorelix, Zoladex or their derivatives,

4. Use as claimed in one of claims 1 to 3, wherein the LHRH analog or combination of LHRH analogs is orally bioavailable.

5. Use as claimed in one of claims 1 to 4, wherein the LHRH analog is a non-peptidergic LHRH agonist or antagonist.

6. Use as claimed in one of claims 1 to 5, wherein the antiestrogen is of the Raloxifen type.

7. Use as claimed in one of claims 1 to 6, wherein the two active ingredients are present in separate forms of administration.

8. Use as claimed in one of claims 1 to 6, wherein the two active ingredients are present in separate forms of administration.

9. Use as claimed in claim 7 or 8, wherein the LHRH analog and antiestrogen are used at the same time and/or sequentially in time.

Article 34

091733 092290



The invention relates to a pharmaceutical combined preparation of LHRH analogues and anti-oestrogens having tissue-selective oestrogen activity and also to its use for the treatment of gynaecological disorders, especially for the treatment of endometrioses and myomas.

Docket No.  
SCH 1655

# Declaration and Power of Attorney For Patent Application

## English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

**Pharmaceutical Combined Preparation and Its Use in the Treatment of Gynaecological Disorders**

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on 29 January 1997 as United States Application No. or PCT International Application Number PCT/EP97/00395

and was amended on 21 April 1998 and 28 July 1998

(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Priority Not Claimed

|                             |                             |                             |                          |
|-----------------------------|-----------------------------|-----------------------------|--------------------------|
| <u>196 04 231.3</u>         | <u>Germany</u>              | <u>29/01/1996</u>           | <input type="checkbox"/> |
| (Number)                    | (Country)                   | (Day/Month/Year Filed)      |                          |
| <u>                    </u> | <u>                    </u> | <u>                    </u> | <input type="checkbox"/> |
| (Number)                    | (Country)                   | (Day/Month/Year Filed)      |                          |
| <u>                    </u> | <u>                    </u> | <u>                    </u> | <input type="checkbox"/> |
| (Number)                    | (Country)                   | (Day/Month/Year Filed)      |                          |

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112. I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

\_\_\_\_\_  
(Application Serial No.)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Status)  
(patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. (list name and registration number)

I. William Millen (Reg. No. 19,544)  
 John L. White (Reg. No. 17,746)  
 Anthony J. Zelano (Reg. No. 27,969)  
 Alan E.J. Branigan (Reg. No. 20,565)  
 John R. Moses (Reg. No. 24,983)  
 Harry B. Shubin (Reg. No. 32,004)  
 Brion P. Heaney (Reg. No. 32,542)  
 Richard J. Traverso (Reg. No. 30,595)

Diana Hamlet-King (Reg. No. 33,302)  
 John A. Sopp (Reg. No. 33,103)  
 Richard E. Kurtz (Reg. No. 33,936)  
 Richard M. Lebovitz (Reg. No. 37,067)  
 John H. Thomas (Reg. No. 33,460)  
 Luan Cao Do (Reg. No. 38,434)

Send Correspondence to: MILLEN, WHITE, ZELANO & BRANIGAN, P.C.  
Arlington Courthouse Plaza I  
2200 Clarendon Blvd., Suite 1400  
Arlington, VA 22201

Direct Telephone Calls to: (name and telephone number)  
Anthony J. Zelano (703-812-5311)

|  |            |
|--|------------|
| Full name of sole or first inventor<br><b>Klaus STÖCKEMANN</b> | V 08/18/98 |
| Sole or first inventor's<br><i>[Signature]</i>                 | Date       |
| Residence<br><b>Berlin, Germany DEX</b>                        |            |
| Citizenship<br><b>Germany</b>                                  |            |
| Post Office Address<br><b>Holsteinische Strasse 33a</b>        |            |
| <b>D-12161 Berlin, Germany</b>                                 |            |

|   |          |
|---|----------|
| Full name of second inventor, if any<br><b>Peter MUHN</b> |          |
| Second inventor's signature<br><i>[Signature]</i>         | Date     |
| Residence<br><b>Berlin, Germany DEX</b>                   | 24/08/98 |
| Citizenship<br><b>Germany</b>                             |          |
| Post Office Address<br><b>Markgrafenstrasse 61</b>        |          |
| <b>D-13465 Berlin, Germany</b>                            |          |